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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,166	08/17/2001	Melwyn A. Abreo	0125-0043	1466

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EXAMINER

MCKENZIE, THOMAS C

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 07/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/931,166

Applicant(s)

ABREO ET AL.

Examiner

Thomas McKenzie, Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 17 August 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-54 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 33-36, 38-41 and 47-50 is/are allowed.
- 6) ☒ Claim(s) 1, 7, 14, 19-23, 37, 42-46 and 54 is/are rejected.
- 7) ☒ Claim(s) 2-6, 8-13, 15-18, 24-32 and 51-53 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>2/02</u> .  | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

1. This action is in response to an application filed on 8/17/01. There are fifty-four claims pending and fifty-four under consideration. Claims 1-36 and 51-53 are compound claims. Claims 37-41 are composition claims. Claims 42-50 and 54 are method of using claims. This is the first action on the merits. The application concerns some Pyrazolo[3,4-d]pyrimidine and Pyrazolo[4,3-c]pyridine compounds, compositions, and uses thereof.

#### **Title**

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: addition of the word "Fused" to the beginning of the present title.

#### ***Specification***

3. The attempt to incorporate subject matter into this application by reference to Binstock et al., Methods Enzymol., 71, 403-411, 1981 on page 100 is improper because this is essential material for anyone trying to practice Applicants invention. This assay is mandatory for assaying Applicants compounds. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory

material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify “a disease or condition mediated by ERAB, HADH2, or amyloid-β”. It is unclear what diseases and treatments applicant is intending to encompass. Determining whether a given disease responds or does not respond to such an enzyme inhibitor and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. Without such clinical research to identify the patients and diseases Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claim is indefinite.

5. Claim 45 recites the limitation "cancer" in line 1. There is no antecedent basis for this limitation in parent claim 42. Cancer is not presently understood to be "a disease or condition mediated by ERAB, HADH2, or amyloid- $\beta$ ".

**Claim Rejections - 35 USC § 112**

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7, 14, 19-23, 37, 42-46, and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs or metabolites of the claimed compounds. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Finding a prodrug or a metabolite is an empirical exercise. Predicting if a

certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science.

b) The direction concerning the prodrugs and metabolites is found in lines 24-27, page 22. c) There is no working example of a prodrug or metabolite of a compound the formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the

prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim 1 as well as the presently unknown list potential prodrug derivatives embraced by claim 1.

Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

7. Nowhere in the specification are directions given for preparing the "prodrugs" or "metabolites" of the claimed compounds. Since the structures of these "prodrugs" are uncertain, direction for their preparation must also be unclear.

Directions to a team of synthetic pharmaceutical chemists and metabolism experts of how to search for a "prodrug" or a "metabolite" hardly constitute instructions to the BS process chemist of how to make such a compound.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-45 and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating any human disease. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered in making an enablement rejection were summarized above. The three main issues are the lack of any correlation between clinical efficacy for any disease treatment and Applicants' single *in vitro* ERAB enzyme assay, the state of the prior art, and the breadth of the claims.

There is an *in vitro* assay described in pages 100-105 with data on twenty-eight compounds. It is a bit confusing for Applicants state that the enzymatic reaction is run in the reverse direction but the Examiner assumes that Applicants



compounds inhibit, not promote, this reaction. Applicants do not state and it is not recognized in the clinical arts this assay is correlated to efficacy for treatment of any diseases. The state of the clinical arts in ERAB enzymology is provided by Wen (Brain Research) who states in the last sentence of section 32, page 117 the enzyme HSD-10, called by Applicants ERAB, is not present in the plaques of brains taken from human Alzheimer's patients. How can inhibition of an enzyme not found in Alzheimer's patients have any effect on the disease? Ofman (Am. J. Hum. Genet.) states in the final paragraph, page 1305, "[t]he link among MHBD, Alzheimer disease, and the neurodegeneration observed in patients with MHBD deficiency remains unclear." MHBD deficiency is caused by mutations in the *HADH2* or ERAB gene. He further states, "that deposition of Alzheimer vascular amyloid- $\beta$  is associated with *decreased* rather than *increased* expression of brain ERAB".

The scope of the claims involves all of the thousands of compounds of claim 1, the unknown list of diseases embraced by the phrase "a disease or condition mediated by ERAB, *HADH2*, or amyloid- $\beta$ ", as well as the hundred of diseases embraced by the term cancer. Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the

time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.


***Allowable Subject Matter***

9. Claims 33-36, 38-41, and 47-50 are allowed. Claims 2-6, 8-13, 15-18, 24-32, and 51-53 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Conclusion***

10. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

11. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

  
**Thomas C. McKenzie, Ph.D.**  
**Patent Examiner**  
**Art Unit 1624**

TCMcK/me